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SULFHYDRYL COMPOUNDS IN THEORY AND PRACTICE

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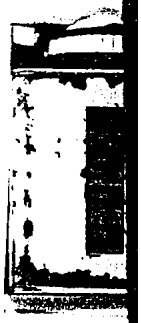
In contemporary physiology and biochemistry, a special place is occupied by the investigation of the role of sulfhydryl compounds and the dynamics of their reversible transformations in the course of various normal and pathological processes.

During the past 20 years this problem has acquired a certain urgency in the laboratories of many countries, because it is organically connected with cardinal problems of biology which have a bearing on present-day needs of practical medicine and toxicology. The two lines of investigation mutually supplement each other. The structural entities forming proteins are characterized by the presence of so-called reactive or functional groups, among which the sulfhydryl groups occupy a special place. In investigations carried out from this standpoint, biochemists have demonstrated the dependence of the activity of the main quantity of enzymes active in the body, particularly that of the important active agent coenzyme A, on the condition of the sulfhydryl groups.

Physiological investigations conducted during the past 10 years by the author of this article and a group of co-workers at the Academy of Sciences USSR and at Moscow University have shown the great dependence of many physiological phenomena on the condition of the sulfhydryl groups. These investigations represent a further development based on the enzyme-chemical hypothesis of processes of nerve stimulation and inhibition. We have shown the possibility of the occurrence of reversible changes in the movement of paramecia in response to an electric irritation (galvanotaxis) and in the reaction to light (phototaxis) of invertebrate animals as a result of the blocking and subsequent liberation of sulfhydryl groups. The reversible blocking and binding of these groups changes not only the sensitivity to an electric irritation in paramecia, but also the summary reactions in actinia.

The dependence of the glowing of marine animals of the genus Noctinaluca on the condition of the sulfhydryl groups was established. It has been found that the periodic motor reaction which occurs in actinia under the effect of various influences can be interrupted by blocking sulfhydryl groups and restored by introducing new sulfhydryl groups. The dependence of bioelectric phenomena on these groups was also established. Thus, the rest current of the sartorius muscle can be observed when substances that block the sulfhydryl groups are applied to one of the ends of this muscle. The current which originates under these conditions disappears after repeated treatment of the region in question with cysteine (S. Oganesyan). The normal electrical activity of the heart is modified sharply and reversibly when the tissue sulfhydryl groups have been blocked (K. S. Logunova).

One may temporarily stop the rhythmic activity of the heart by blocking sulfhydryl groups of the cardiac tissue. The activity of the heart is restored when substances are introduced into it which either contain free sulfhydryl groups or contribute to the liberation of these groups from tissue proteins and to their activation. Both the activity of the vagus and the effect of acetylcholine on the cardiac activity depend to the fullest extent on the condition of the tissue sulfhydryl groups. Binding of these groups results in inhibition of the activity of the vagus and of the action of acetylcholine, while their restoration to the original state leads to a reactivation of the functions mentioned.



The fatigue of muscles which results from an indirect irritation may be removed by the action of drugs which contain sulfhydryl groups (cysteine) and also of substances which contribute to the liberation and activation of reserve sulfhydryl groups (urea and guanidine). These groups play a role in the transmission of stimuli not only at peripheral but also at central synapses. By bringing about reversible blocking and restoration of sulfhydryl groups one may modify the sensitivity of receptors of the intestine, blood vessels, and sense organs of vertebrates and insects.

The use of a number of tracer atoms (cf. work by T. M. Turpayev) and of some histochemical methods have enabled us at present to acquire a deeper knowledge of the dynamics of transformations of tissue sulfhydryl groups.

Numerous experimental investigations have shown that at all stages of the functioning of the reflex apparatus the condition of the sulfhydryl groups of natural thiol compounds (various protein complexes, primarily enzymes, glutathione, etc.) plays an important role. As a rule, the blocking of these groups interferes with reflex processes and with neuro-humoral effects, while the restoration of these groups removes the temporary interference with nervous reflex processes.

In view of the fact that the basic phenomena involved take place within the fine structure of protein complexes, the general conclusion may be drawn that neurohumoral regulation in the body is brought about by means of a thorough-going interaction between proteins and enzyme-chemical processes connected with them, on the one hand, and the functioning of neurohumoral agents on the other hand.

The phenomena described above can be observed not only on isolated organs, but also on whole animals. For instance, a complete stoppage of cardiac activity and of reflex actions in frogs takes place when substances have been introduced which block sulfhydryl groups (e. g., cadmium chloride). Restoration of the functions of the heart and of the nervous system takes place when sulfhydryl compounds, for instance cysteine, have been introduced. Similar experiments have been carried out on warm-blooded animals.

Lately we have obtained in work carried out in cooperation with Sh. A. Galoyan experimental proofs of the dependence between the conditioned reflex activity of warm-blooded animals and the condition of their tissue sulfhydryl groups. It has been found that a number of firmly established positive conditioned reflexes and differentiations in rats (according to the method of L. I. Kotlyarevskiy) disappear after administration to the animals of definite quantities of cadmium chloride. However, when the rats at the same time receive substances containing sulfhydryl groups, the conditioned reflexes and differentiations which have been developed are not modified. Conditioned reflexes which disappear for 3-4 days as a result of the action of cadmium chloride are restored spontaneously, evidently because of the mobilization of sulfhydryl groups already present in the organism.

The numerous morphological investigations carried out by A. I. Smirnova-Zamkova have a direct bearing on the problem under consideration. These investigations deal with the so-called argyrophilic substance, which reacts with a great deal of sensitivity to various pathological changes in the organism. In Smirnova-Zamkova's opinion, the argyrophilic substance corresponds to the reactive groups of proteins, particularly their sulfhydryl groups.

It follows from this that biochemical, physiological, and morphological data clearly indicate that thiol compounds (i. e., sulfhydryl groups) are of great importance for the occurrence of vital processes. For this reason they are of great importance for practical medicine.

The development of the first synthetic thiol compound, i. e., 2, 3-dimercaptopropanol, otherwise called British Antilewisite (BAL), was a result of a search for substances which would counteract the toxic action of lewisite. The beneficial action of BAL in counteracting a number of other toxic agents was established. Specifically, it has been shown that mercury-organic compounds lower the activity of the sulfhydryl groups and that the application of BAL exerts a therapeutic effect following poisoning with mercuric chloride.

Later the great usefulness of thiol compounds, particularly BAL, in exerting an effect on profound disturbances of metabolism was established. For instance, it has been shown that in the so-called experimental alloxane diabetes, which develops as a result of a disturbance of the normal dynamics of the transformation of sulfhydryl groups in the body, introduction of thiol compounds brings about normalization of metabolism and elimination of the symptoms of the disease.

As the experience of foreign and USSR neuropathologists and psychiatrists has shown, drugs which contain sulfhydryl groups are effective in the treatment of some acute disturbances of the functioning of the central nervous system, particularly when the hepatolenticular syndrome is present. The opinion is held that the pathogenesis of the hepatolenticular syndrome and the conditions which accompany it are caused by disturbances in the distribution of copper in the organism following a primary disturbance of the functioning of the liver and a consequent accumulation of copper in the nuclei of the strio-pallidal region. It is known that copper is one of the thiol poisons. The pathological process which develops apparently takes place as a result of a disturbance of the metabolism of the nuclei of the striopallidal region. This disturbance develops because the sulfhydryl groups have been blocked. Administration to patients suffering from a hepatolenticular syndrome of drugs which contain thiol groups (2, 3-dimercaptopropanol or unithiol) produces a good therapeutic effect. This has been confirmed by data obtained at the neurological clinic directed by Prof A. M. Grinshteyn.

Investigations carried out by us in collaboration with T. A. Speranskaya have shown that sulfhydryl substances are definitely effective in overcoming the neurotoxic action of streptomycin. In several series of experiments it has been found that animals which have received streptomycin for a long time develop at a definite point pronounced disturbances of motor coordination that are of vestibular origin. The control animals which have received streptomycin for a much longer time, but also were administered sulfhydryl drugs, did not develop any pathological changes. These data, which have been obtained in systematic animal experiments, have been confirmed by the observations of Belgian scientists. The Belgian scientists have shown that specific cytochemical changes in the ganglionic cells of the inner ear which take place as a result of the action of streptomycin are absent when streptomycin is administered together with sulfhydryl drugs (Unithiol, cystamine).

A special place among substances which contain sulfhydryl groups is occupied by the complex iron-containing protein ferratin, which was discovered by the Czech scientist V. Laufberger in 1937. At our laboratory M. M. Konstantinova obtained this substance in a crystalline state and then, after restoring the sulfhydryl groups of the ferratin with the aid of glutathione, investigated its action on animals suffering from experimental renal hypertension. It turned out that in these animals ferratin in very small doses is capable of bringing about a sharp lowering of the blood pressure. For instance, the blood pressure of rabbits dropped by 15-120 millimeters of mercury when 0.3 milligrams of ferratin had been administered per kilogram of animal weight.

However, ferratin which contains sulfhydryl groups exerts a hypotensive action only on animals that have an excessive blood pressure. It is particularly effective during the second chronic stage of hypertension. Under normal conditions ferratin has no effect on the blood pressure.

A number of investigators used as hypotensive agents in animal experiments and at the clinic other sulfhydryl drugs (glutathione, cystamine, BAL, mercaptopropionic acid, etc.) However, the effective dose of ferratin is almost 100 times smaller than that of the other sulfhydryl substances mentioned.

Many foreign scientists are paying great attention to the use, as a hypotensive agent, of ferratin containing active sulfhydryl groups. This substance does not produce any complications. Being a product of metabolism, it constantly participates in the compensatory functions taking place within the organism, particularly functions which regulate disturbances of the hemodynamics. Recent investigations carried out by the American scientists Mazur, Shor, and others on the subject, which deal with the fine intramolecular relationships between iron and sulfhydryl groups in the complex molecule of ferratin as they are affected by various changes of metabolism, open up new perspectives.

It has been established that the action of some cancerogenic agents is suppressed when sulfhydryl compounds are administered to experimental animals simultaneously with these agents. Research in this promising field of theory and practical applications is of particular importance and interest.

The problem in regard to the role played by sulfhydryl groups in the organism and the possibilities of using drugs containing sulfhydryl groups in practice has acquired a particular importance in connection with the investigation of the causes of radiation sickness and with work aiming at the development of efficient means of counteracting pathogenic effects produced by radiation.

The data cited by us indicate the importance of further investigations of the physiological role and practical applications of sulfhydryl compounds. In work conducted in this field cooperation between physiologists, biochemists, pharmacologists, and clinicists is essential.

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